GENERAL PRACTICE IN CHINA

Research Progress in Epidemiology and Risk Factors of Primary Liver Cancer

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Recommended Citation

CHEN Q Q，RUI F J，NI W J，et al. Research Progress in Epidemiology and Risk Factors of Primary Liver Cancer［J］. Chinese General Practice，2023. ［Epub ahead of print］.

DOI：10.12114/j.issn.1007-9572.2023.0479.

Available at： https：//gpinchina.net

Research Progress in Epidemiology and Risk Factors of Primary Liver Cancer

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【**Abstract**】 Primary liver cancer is one of the most common cancers in the world and with extremely high morbidity and mortality. This paper details the current epidemiology of primary liver cancer，population attributable fractions and associated risk factors in China. In this paper，we found that hepatitis B virus and hepatitis C virus are still the main risk factors for the development of primary liver cancer by searching the databases such as PubMed，Web of Science，and CNKI. With hepatitis B virus vaccination and antiviral treatment，the incidence of primary liver cancer in China has slightly decreased，but the incidence of primary liver cancer caused by metabolic factors such as diabetes，obesity and non-alcoholic fatty liver disease is gradually increasing；smoking and alcohol consumption are also important risk factors. This article summarizes the epidemiological characteristics and risk factors of primary liver cancer，which can provide practical evidence-based medicine evidence for the development of preventive and control measures for primary liver cancer.

【**Key words**】 Liver neoplasms；Primary liver cancer；Epidemiology；Risk factors；Population attribution fraction；Review

Primary Liver Cancer （PLC） is the sixth most common malignant tumor worldwide and the third most common cause of cancer-related deaths[1]. PLC mainly includes hepatocellular carcinoma （accounting for 75%-85%） and intrahepatic cholangiocarcinoma （accounting for 10%-15%）. In 2020, there were approximately 905 677 new cases of PLC globally, with a high death toll reaching 830 180[1]. The highest incidence of PLC is found in Asia and Africa[2], with China accounting for about half of all PLC patients worldwide[3]. Currently, PLC ranks as the fourth most common malignant tumor and the second leading cause of cancer-related deaths in China, posing a severe threat to people's life and health[4]. A comprehensive understanding of the epidemiological characteristics and risk factors of PLC is of significant importance for its prevention and treatment. This article reviews the epidemiological features and risk factors of PLC in China, aiming to provide reference and insights for the prevention

and treatment of PLC in the country.

1 Literature Search Strategy

A computerized search of databases including PubMed, Web of Science, and CNKI was performed from inception to March 2023. For the search, we used Chinese keywords such as "primary liver cancer", "epidemiology", "risk factors", and "population attribution fraction". The English equivalents used were “primary liver cancer,” “epidemiology,” “risk factors,” and “population attribution fraction.”We excluded publications that were not related to the topic of this paper, were of low quality, or where the full text was inaccessible. In total, 64 articles were included in this paper for review.

2 Epidemiology of PLC

2.1 Incidence and Mortality Rates of PLC

In China, the age-standardized incidence rates （ASIR） and age-standardized mortality rates （ASMR） for primary liver cancer （PLC） are 17.81/100,000 and 15.29/100,000 respectively. The total annual incidence and mortality cases of PLC in China account for about half of the global cases, with significant urban-rural and regional differences[5]. The ASIR （20.07/100,000） and ASMR （17.52/100,000） in rural areas are higher than those in urban areas （ASIR: 16.13/100,000 and ASMR: 13.64/100,000）, especially among the population under 65 years of age[5]. Geographically, the western underdeveloped regions have the highest ASIR and ASMR, followed by the central and eastern regions[5], as shown in table 1. Studies indicate a 58.5% decline in ASIR of PLC in 2019 compared to 1990, potentially related to the reduction in the prevalence of hepatitis B virus （HBV） and hepatitis C virus （HCV） infections and exposure to aflatoxins[6].

2.2 Demographic Characteristics of PLC

The incidence of PLC is closely related to age[7]. The incidence rate of PLC in China gradually increases with age. It is relatively low for those under 30 and starts to rise rapidly for those aged 30 and above, peaking in the 80-84 age group[8]. Moreover, the average age of PLC onset has been increasing year by year. For males in rural and urban areas, the average age of onset increased from 56.53 and 59.67 in 2000 to 61.20 and 62.66 in 2014, respectively. For females, it delayed from 60.60 and 65.50 to 66.07 and 69.87[9].

Globally, male PLC incidence and mortality rates are 2-3 times higher than females[1]. In China, males have significantly higher PLC incidence and mortality rates than females[8], likely due to different exposures to risk factors. Research shows that the prevalence of viral hepatitis, smoking, and drinking is higher in males than females[10]. Another study reveals that the levels of estrogen/androgen are associated with the reduction/increase in HBV

transcription and replication, possibly explaining why inflammation-driven PLC incidence is higher in male HBV-infected patients than females[11].

2.3 Population Attributable Fraction （PAF） of PLC

PAF is defined as the proportion of cancer burden attributable to risk factors in the target population[12]. Globally, 33%, 21%, and 30% of PLC cases are attributed to HBV infection, HCV infection, and alcohol consumption, respectively[13]. Given the diverse risk factors for PLC across different countries and regions, PAF varies accordingly. In China, 72.4% of deaths related to PLC are attributed to risk factors including HBV and HCV infections, smoking, drinking, diabetes mellitus （DM）, obesity, and others[10]. HBV has the largest share in the burden of PLC among both Chinese men and women; the PAF for smoking, drinking, and DM is significantly higher in men than in women, but women have a higher obesity PAF compared to men[10], as shown in table 2.

PAF varies by age as well. In men, HBV-induced PLC has the largest PAF across all age groups, while the PAF for smoking and drinking induced PLC decreases with age[10]. In women of all age groups, HBV-induced PLC also has the largest PAF. The PAF for HCV-induced PLC in both men and women increases with age. For those aged 60 and above, the PAF for DM, drinking, and smoking is higher than for those under 60[10]. Therefore, active promotion of hepatitis B vaccination, expansion of antiviral treatments, and adherence to healthy lifestyles are the primary preventive measures for PLC in China[14].

3 Primary Liver Cancer （PLC） Risk Factors

Common risk factors for PLC include chronic HBV and HCV infections, alcoholic liver disease, and metabolic diseases, such as non-alcoholic fatty liver disease （NAFLD）, diabetes mellitus （DM）, etc[15]. Although antiviral drugs can control and even cure chronic HBV and HCV infections to some extent, chronic viral infections remain the primary cause of PLC in China[16]. Additionally, with the increasing population of individuals with obesity and DM, the prevalence of metabolic syndrome（MetS） and NAFLD will further lead to a rise in PLC incidence[17].

3.1 HBV Infection

HBV infection is a significant risk factor for PLC in China. It can promote the development of PLC through direct and indirect mechanisms. On the one hand, HBV can lead to chromosomal remodeling and abnormal expression of oncogenes and tumor suppressor genes, such as CTNNB1, TP53, Axin1, and RB1, by integrating or inducing host gene mutations[15]. It can also activate tumor-associated signaling pathways, regulate cellular metabolism, and promote the occurrence of PLC[16-17]. On the other hand, HBV can cause chronic liver inflammation and changes in the liver microenvironment, promoting the progression from inflammation to cancer [16]. According

to data from the Global Burden of Disease 2019, there were about 23 355 000 people infected with HBV, with approximately 140 000 new cases of HBV-related liver cancer[18]. The lifetime risk of PLC in HBV-infected patients is around 10%-25%[19]. HBV vaccination is key in preventing and reducing PLC[20]. Antiviral treatment is also an effective measure to reduce the risk of PLC[21].

3.2 HCV Infection

Various mechanisms could lead to HCV-related carcinogenesis, including the inhibition of apoptosis pathways by telomerase activity and HCV core protein, cell cycle dysregulation caused by NS5B, and activation of growth pathways by NS3/4A[22]. In 2019, there were about 625 000 cases of HCV infection in China, with approximately 34 000 new cases of HCV-related PLC[18]. The prevalence of PLC in HCV-infected patients is 2% to 4% once they have progressed to the stage of cirrhosis[23].Antiviral treatment achieving sustained virological response can significantly reduce the risk of HCV-associated PLC[24-25]. There is no reference guideline to stop monitoring patients initially included in PLC monitoring[26].

3.3 Smoking

Cigarettes contain over 4 000 harmful substances, including nicotine, which can bind to DNA and induce genetic mutations, increasing the risk of malignant tumors[27]. Current smokers in China have a 28% higher risk of developing PLC compared to non-smokers[28]. Quitting smoking for many years is negatively correlated with the risk of PLC, and those who quit for 30 years have a risk similar to those who never smoked[29].

3.4 Alcohol Consumption

Excessive alcohol consumption is a recognized risk factor for PLC [30]. Mechanisms include direct damage to proteins and DNA by acetaldehyde formation, increased production of reactive oxygen species（ROS）and impaired DNA repair mechanisms, chronic inflammation induction, and changes in gene expression due to interference with methylation[31].

A meta-analysis showed that the cumulative prevalence of PLC in patients with alcohol-related cirrhosis was 1%, 3%, and 9% at 1-, 5-, and 10-year follow-up, respectively[32]. Heavy alcohol consumption （≥3 drinks/d）increases the risk of PLC by 16% in the general population[33]. Controlling and reducing the duration of alcohol consumption helps prevent PLC, especially in individuals over 30 years old and in high-risk cancer groups[34]. The higher the amount of alcohol consumed and the longer the number of years of drinking, the higher the risk of PLC[34]. Meanwhile, this study also showed that controlling alcohol consumption and reducing the number of years of drinking can help to prevent the occurrence of PLC, especially for people >30 years of age and people with a high prevalence

of cancer, who should reduce the intake of alcohol[34]. In addition, alcohol also contributes to the occurrence and development of PLC together with other risk factors. A prospective study showed that alcohol consumption and obesity increased the risk of PLC risk （*HR*=3.82）[35]. In patients with alcohol-related cirrhosis, the risk of PLC was 50% higher in patients with combined DM than in those without combined DM [30]. Therefore, screening for DM in heavy drinkers should be strengthened to identify patients at high risk of PLC.

3.5 Metabolic-Related Risk Factors

3.5.1 DM DM increases the risk of PLC through mechanisms like insulin resistance, increased free radicals, and impaired liver cells, compensatory hyperinsulinemia causing fatty liver and liver fibrosis, and increased secretion of insulin-like growth factor-1 inducing cell proliferation and inhibiting apoptosis[36]. DM is associated with a 2-3 times higher risk of PLC, and men have a significantly higher relative risk than women[37]. A meta-analysis of prospective studies showed that longer duration of DM was associated with an increased risk of PLC[38]. In addition, DM is strongly associated with NAFLD. Studies have shown that DM is an important metabolic risk factor for the development of PLC in patients with NAFLD[38]. Studies have shown that DM is an important metabolic risk factor for the development of PLC in patients with NAFLD[39]. Among patients with NAFLD-related liver cirrhosis, the risk of PLC was 4.2 times higher in patients with DM than in patients without DM[40]. A study of 85 000 patients with comorbid DM followed for an average of 10 years showed that patients with comorbid DM had a 24% higher risk of PLC compared with those without DM （*HR*=1.24）, patients with good glycemic control had a 32% （*HR*=1.24） lower risk of PLC compared with those with poor glycemic control[41].

3.5.2 Obesity Obesity promotes PLC through mechanisms like oxidative stress and cell damage caused by liver cells exposure to excess lipids, chronic inflammation due to adipose tissue secretion of various adipokines, and the induction of an immune-tolerant microenvironment[42,45-46]. A meta-analysis of the general population showed that obesity

increases the risk of PLC approximately twofold[47]. Cohort studies in the United States have shown that Individuals with a large waist circumference （defined as ≥ 110 cm for men and ≥ 90 cm for women） have a 2-fold increased risk of developing PLC[48]. In addition, obesity may also increase the incidence of PLC in patients with chronic liver disease. A Chinese study of patients with chronic HBV A Chinese study of patients with chronic HBV reported that central obesity （defined as waist circumference/waist height） was associated with a higher risk of PLC compared with non-central obesity[47]. A Chinese study of patients with chronic HBV reported that central obesity （defined as waist/height >0.5） was associated with an increased risk of PLC （*HR*=1.63）[49]. In addition,

obesity is closely associated with NAFLD, which contributes to the development of PLC[50].

3.5.3 MetS MetS is a risk factor for PLC and includes abdominal obesity, high triglyceride lipids, low HDL cholesterolemia, hypertension, and hyperglycemia. A prospective study with a median follow-up time of 13.02 years showed that the risk of PLC in patients with MetS was 2.91 times higher than that in patients without MetS[51]. Another cohort study based on a population in Taiwan showed that the risk of PLC was 2.91 times higher in patients with MetS than in those with non-MetS[51]. The risk of PLC in patients with MetS and NAFLD was 15.33 times higher than that in the control group （non-MetS and non-NAFLD patients）[52].

3.5.4 NAFLD Potential mechanisms by which NAFLD increases the risk of PLC development include: （1） obesity, DM, and other metabolic factors that cause chronic liver inflammation, increased hepatic lipotoxicity, insulin resistance, and hyperinsulinemia, this induces apoptosis and activates immune and inflammatory pathways leading to the development of NAFLD and hepatic fibrosis, resulting in the development of NAFLD[53]. （2） The dysbiosis of intestinal flora is mediated by intestinal mucosal barrier disruption, bile acid signaling toll-like receptor agonism and other mechanisms that promote the development of PLC[54]. （3） Mutations in PNPLA3 lead to impaired hydrolysis of triglycerides and increased free fatty acid synthesis, which promote PLC[55]. With the spread of obesity and MetS, the incidence of NALFD-induced PLC has been increasing year by year[56]. A study found that the incidence of PLC in patients with NAFLD was 0.21/1,000 persons/year, which was significantly higher than that in patients without NAFLD[57]. For each additional metabolic factor （including DM, obesity, dyslipidemia, and hypertension）, the risk of PLC in patients with NAFLD increased. NAFLD patients with DM have a 2.77 times higher risk of progression to PLC than non-DM patients[58].

3.6 Other Factors

Aflatoxins are a group of carcinogenic substances produced by fungi such as Aspergillus flavus and Aspergillus parasiticus. Aspergillus parasiticus and other fungi, aflatoxin B1 （AFB1） is the most toxic and carcinogenic substance[59]. On the one hand, AFBl can induce acute hepatic necrosis, leading to cirrhosis or PLC[60]. On the other hand, AFBl metabolites can bind DNA and alkylated bases through epoxide metabolites[61], inducing cell cycle disorders and p53 mutations, and increasing the risk of PLC. Since 1985, the policy of allowing rice to replace maize has resulted in a 40-fold reduction in aflatoxin-albumin adducts, which has led to a decrease in PLC in China[62]. Microcystin （MC）, a hepatotoxic metabolic product secreted by blue-green algae, is commonly found in freshwater lakes and drinking water. MC induces PLC by inhibiting protein phosphatases 1 and 2A, leading to the excessive phosphorylation of intermediate filaments and microfilaments, and liver cell skeleton damage[63]. Studies have shown

that cyanobacteria account for less than 1% of the total oral microbiota group was less than 1%, and after correcting for well-established risk factors for PLC, cyanobacteria were found to be positively associated with PLC[64].

4 Summary and Outlook

Currently, HBV and HCV infections remain the most significant risk factors for PLC. With the vaccination against HBV, effective antiviral treatments for patients infected with HBV and HCV, and screening of high-risk populations for viral hepatitis, the prevalence of viral hepatitis is expected to decline. Obesity, DM, NAFLD, and excessive alcohol consumption are increasingly becoming important risk factors for the occurrence of PLC. Promoting healthy lifestyles, enhancing the screening, prevention, and treatment of metabolic diseases like NAFLD, improving and refining PLC monitoring and treatment strategies will significantly enhance the level of PLC prevention and treatment in China. This improvement is anticipated to comprehensively reduce the social, economic, and medical burdens of PLC in the country in the future. However, there are still urgent issues that need to be researched and addressed:（1）There is a lack of specific biomarkers and monitoring methods for early identification of PLC. （2） There is a shortage of convenient tools for stratifying high-risk populations for PLC, for example, the development of self-monitoring apps could be a potential solution. （3） There is a lack of effective treatments for NAFLD.

Authors' contributions: Chen Qianqian was responsible for the conception and design of the article, collection and organization of research data, plotting tables, and writing the paper; Rui Fajuan and Ni Wenjing were responsible for the revision of the paper; Li Jie was responsible for the conception and design of the article, the revision of the paper, the quality control of the article, and proofreading of the article, and was responsible for overall responsibility for, and supervision and management of, the article.

There is no conflict of interest in this paper.

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